RECIST 1.1: Applying the Rules

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Background

- Initial attempts to standardize assessing tumor response began in 1960s

- 1979 World Health Organization
  - Standardized criteria for response assessment

Problems with WHO criteria

- Interpretation of WHO guidelines vary amongst groups
- Minimum lesion size number of lesions to be recorded vary
- Definition of progressive disease (PD) varied
- Maturation of imaging technology not taken into consideration
- Discrepancies identified during independent review

Development of RECIST 1.0

- 1994 international task force
  - European Organization for Research and Treatment of Cancer (EORTC)
  - National Cancer Institute (NCI) of the U.S.
  - National Cancer Institute of Canada Clinical Trials Group
- Review of 4000 patients for tumor response
- Recommendation to simplify response evaluation
- 1999: Criteria was publicly presented/accepted the American Society for Clinical Oncology meeting
- 2000: Published in *Journal of the National Cancer Institute* in 2000
- Intended for solid tumor response assessment in Phase II clinical trials but is actually being used for response assessment in all Phases

RECIST Version 1.1

- Working group call together again CTG
- Use evidence-based approach:
  - Literature
  - Data analysis
- Proposed changes distributed for comments
- Revised RECIST 1.1 published January 2009

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New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

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Measurability of Tumor at Baseline

- Measurable disease
- Non-measurable disease

Measurable Disease

- Tumor lesion measured in longest diameter
  - ***EXCEPT*** for lymph nodes: use short axis
- Minimum size of measurable non-nodal lesions
  - CT scan 5 mm slice: ≥10 mm
  - CT scan > 5 mm slice: 2x slice thickness
  - Calibers (clinical exam): ≥10 mm
  - Chest x-ray: ≥20 mm
- Up to 5 measurable lesions (2/organ)

Non-measurable Disease

- All other lesions
- Includes:
  - Bone lesions
  - Leptomeningeal disease
  - Ascites
  - Pleural/pericardial effusion
  - Inflammatory breast disease
  - Cystic lesions

Tumor Response Evaluation

- Overall tumor burden at baseline including lymph nodes
  - Target lesions
  - Non-target lesions

Target Lesions

- All measurable lesions up to 5 total (max of 2/organ)
  - Must be representative of all involved organs
- Selected on the basis of their size and suitability for accurate repeated measurements
- Sum of diameters

Non-Target Lesions

- Any lesion or site of disease not classified as a target lesion
- Measurement of the lesions is not required
  - Present
  - Absent
- Can record multiple non-target lesions in same organ as single item on CRF

Assessment of Lymph Node

- Target lesion:
  - Lymph node ≥ 15 mm
- Non-target lesion
  - Lymph node <15 mm
- Normal if lymph node is <10 mm

Response Assessment

- Determine:
  - target lesion response
  - non-target lesion response
  - appearance of new lesions

Target Lesion Response

- **Complete Response (CR)**
  - Disappearance of all target lesions
  - Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm
- **Partial Response (PR)**
  - At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
- **Progressive Disease (PD)**
  - At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study).
  - In addition to the relative increase of 20%, sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
- **Stable Disease (SD)**
  - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Longest Target Lesion Diameter (cm): BL & #1

Lesion	BL	#1
Rt.Lung #1	3	2
Rt.Lung #2	2.5	2
Lt liver lobe	6	5
Rt Liver lobe	2.5	2
Total Length	14	11
% Change		-21%
Disease Status		SD

- 11/14 = 0.79
- 0.79 - 1 = (-0.21)
- (-0.21) x100% = -21%

Not 30% decrease = SD

Longest Target Lesion Diameter (cm): BL, #1, #2

Lesion	BL	#1	#2
Rt.Lung #1	3	2	2
Rt.Lung #2	2.5	2	2
Lt liver lobe	6	5	3
Rt Liver lobe	2.5	2	2
Total Length	14	11	9
% Change		-21%	-36%
Disease Status		SD	PR

- 9/14 = 0.64
- 0.64 - 1 = (-0.35)
- (-0.355) x100% = -36%

PR = > 30% decrease

Longest Target Lesion Diameter (cm): BL, #1, #2, #3

Lesion	BL	#1	#2	#3
Rt.Lung #1	3	2	2	2
Rt.Lung #2	2.5	2	2	2
Lt liver lobe	6	5	3	3
Rt Liver lobe	2.5	2	2	2
Total Length	14	11	9	9
% Change		-21%	-36%	-36%
Disease Status		SD	PR	PR

- 9/14 = 0.64
- 0.64 - 1 = (-0.35)
- (-0.36) x100% =
- -36%

- PR = > 30% decrease

Longest Target Lesion Diameter (cm): BL, #1, #2, #3, #4

Lesion	BL	#1	#2	#3	#4
Rt.Lung #1	3	2	2	2	3
Rt.Lung #2	2.5	2	2	2	3
Lt liver lobe	6	5	3	3	5
Rt Liver lobe	2.5	2	2	2	2
Total Length	14	11	9	9	13
% Change		-21%	-36%	-36%	+44%*
Disease Status		SD	PR	PR	PD
* Change from nadir					

- 13/9 = 1.44
- 1.44 - 1 = (0.44)
- (0.44) x100% = 44%

PD = > 20% increase from nadir

Best Response = PR

Target Lesion: Disease Progression

- ↑20% in sum of target lesions PLUS a 5 mm absolute ↑ over lowest sum
- Guidance on "unequivocal progression" of non-measurable/non-target lesions
  - Overall status of PD and therapy should stop
  - Magnitude of ↑ should be substantial
  - Comparable to ↑ that would be PD for measurable disease

Non-target Lesion Response

- **Complete Response (CR)**
  - Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)
  - Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Non-CR/Non-PD**
  - Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
- **Progressive Disease (PD)**
  - Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions.
  - *Unequivocal progression* should not normally trump target lesion status.
  - It must be representative of overall disease status change, not a single lesion increase.

New Lesions

- Must be unequivocal and not attributed to different scanning technique or non-tumor
- When in doubt, continue to treat and repeat
- If scan showing new lesions is of anatomical region which wasn’t included in BL, it is still PD

Imaging Guidance: FDG-PET

- "–" FDG-PET at BL and "+" at follow-up = PD
- No FDG-PET at BL and "+" at follow-up:
  - PD: corresponds to new site in CT
  - Equivocal: no new site on CT. Repeat CT and if new sit, PD date is that of initial "+" FDG-PET
  - Not PD: corresponds to pre-existing site on CT that is not progressing

Confirmation of Response

- If response is primary endpoint (e.g.,Phase II), confirmation IS required
- If response is secondary endpoint (e.g, RCT w/PFS or OS): confirmation IS NOT required
  - Control arm provides ability to interpret results

Best Response for Patients with Measurable Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment.

Best Response for Patients with Non-measurable Disease

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

RECIST documentation

- Ideally all radiology reports should include tumor measurements but this may not be done using RECIST
- Response needs to be assessed in clinic to make a decision of therapy continuation
  - Measurements should be documented at that time
- CRIS has RECIST documentation flow sheet

Resources

- RECIST version 1.1 resources:
  - http://www.eortc.be/recist/ (link to publications and presentation)
  - http://www.recist.com/